Newborn Screening Technology: Proceed With Caution

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COMMENTARY

Newborn Screening Technology: Proceed With Caution

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THE American College of Medical Genetics (ACMG) recommends a significant expansion in the number of conditions targeted by newborn screening (NBS) programs.[1] In this commentary we advocate a more cautious approach. NBS dates to the early 1960s, when the technology developed to conduct large-scale testing on dried blood spots for phenylketonuria (PKU).[2] PKU remains the paradigm condition for NBS because of features of the disease and its treatment, which are particularly advantageous to population screening. It is a condition that silently causes neurologic devastation but is amenable to early detection and effective prevention with a diet of moderate burden and complexity.[3] Many children affected with PKU and their families have benefited from state screening programs over the past 4 decades because of collaboration between health departments, families, primary care providers, and metabolic specialists.

However, PKU screening is not an unmitigated success.[4,5] There was initial uncertainty about whether children with variant forms of hyperphenylalaninemia required treatment and about whether affected children require life-long dietary management.[6] Indeed, some children with benign conditions were seriously harmed from unnecessary restrictions in their diets.[5] In addition, long-term studies demonstrate decrements in cognitive function for affected children and adolescents who are not fully adherent to the diet,[7,8] yet adherence to the diet is challenging because of its poor palatability, high cost, and limits on insurance coverage in many policies. Affected women who are off the diet are at high risk of bearing severely neurologically impaired children.[9] Only recently have many programs begun tracking affected women to enable notification, education, and management. These difficulties by no means negate the value of NBS for PKU, but they highlight the problems with the successful implementation of a population-based screening program even when a model condition is targeted.

NBS is a system with many elements from blood-spot acquisition to long-term management in the medical home. Any weak links in this chain will impair the efficacy of the program. State health departments continue to struggle to garner adequate resources and expertise to maintain current programs.[2] Other aspects of the NBS system, like insurance coverage for ongoing specialty care and special diets, are beyond health department control. It remains the case in medicine more broadly that population screening of asymptomatic individuals is rarely an effective approach to uncommon diseases.[10–12] Therefore, the onus of responsibility should

Abbreviations: ACMG, American College of Medical Genetics; PKU, phenylketonuria; NBS, newborn screening; HRSA, Health Resources Services Administration; AAP, American Academy of Pediatrics; MS/MS, tandem mass spectrometry

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fall on those who propose population-screening programs for such disorders to marshal the data about benefits and risks and to justify the efforts and expense that these programs entail.

Despite limited data about screening effectiveness in improving health outcomes, NBS programs across the country have added a wide variety of additional conditions over the years, leading to a marked variability in screening panels. [2,13] The trend toward addition of new tests is due, in part, to changes in test technology and to advocacy groups, often supported by family members of affected children who have sought to expand screening in their state for their particular condition. More recently, a number of advocacy groups have collaborated to promote expanded screening at the national level.[14] In 2000, pediatric professional organizations, public health programs, and the federal government evaluated NBS and concluded that a uniform national panel should be developed and reflect the best available data and expert opinion.[2] The ACMG was commissioned by the Health Resources Services Administration (HRSA) to conduct an analysis of the literature and gather expert opinion to provide recommendations for a uniform NBS panel. The final ACMG report was supported promptly by the March of Dimes,[15] the American Academy of Pediatrics (AAP),[16] and the Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children,[17] and many states are adopting its recommendations to promote expanded NBS.

In this commentary we raise 2 sets of concerns with the recommendations of the ACMG report.[18] The first set of concerns focuses on the limitations of the ACMG process. These limitations lead us to conclude that the ACMG report should not be considered definitive and that short-term state and federal NBS policy decisions should be based on a variety of additional considerations. However, we also recognize that new and potentially valuable technologies are available for NBS, such as tandem mass spectrometry (MS/MS), and should not be shelved pending years of research. Rather, we suggest that the new technology be introduced within a research paradigm so that data on efficacy and cost-benefit analyses can inform policy decisions in the foreseeable future. Therefore, our second set of concerns is that programs are expanding rapidly, partly in response to the ACMG report, without the infrastructure in place to determine if the technology is bringing benefits or harms to children.

THE ACMG PROCESS

The recommendations for expanded newborn testing by the ACMG are based primarily on a survey designed to ascertain professional and lay opinions about tests and conditions potentially amenable to NBS. A subsequent assessment of the literature was conducted as a secondary component, in part to validate the results of the survey. Professional and lay opinions can provide valuable information for policy decisions, but without adequate data, opinions provide a weak foundation for new initiatives. Scoring methods for screening and preventive programs, such as those used by the US Preventive Services Task Force[19] and the AAP, identify professional opinion as the weakest form of evidence for policy decisions. This form of evidence is even less persuasive if the relevant opinions are not ascertained in a rigorous fashion.

Survey Design

In the ACMG project, the major tool for ascertainment of opinion was a survey. A survey's value depends heavily on the quality of the analytic framework that guides its design and implementation: the topics addressed in the survey, the wording of the questions, the definition of the population to be surveyed, the selection of a sample from that population, the way the data are analyzed after collection, and the way the data are used in making policy recommendations. In each of these methodologic elements, the process used by the ACMG raises concern. The ACMG survey has no coherent analytic framework. For each of 84 conditions, there are 19 distinct questions. The questions touch on topics relevant to standard criteria for test selection but in an arbitrary way. Some questions ask about objective facts such as the incidence of the condition. Other questions mix fact and value. For example, one question asks the respondent to rank the burden of the untreated condition on a 5-point scale from profound to minimal; to answer, the respondent must combine assumptions about the consequences for the infant with his or her normative judgment about how serious a burden those consequences represent. Not surprisingly, the raw data from the survey demonstrate a high degree of variability even for familiar conditions such as PKU.

The lack of an analytic framework is also evident in the construction of the weights used in aggregating the survey responses to rank conditions. No justification is provided for the weights assigned to different responses on the survey. It is notable that aspects of test methodology were given equal weight with the potential for benefit for affected infants, a methodologic assumption that was not explained in the report and which runs counter to the screening principles that have traditionally justified NBS. For example, 200 points were awarded to a test if it was known to be associated with a life-saving treatment, but a test could also be awarded 200 points if it could be performed on a multiplex machine regardless of whether it had any proven benefits.

In addition, the decision to heavily weigh ancillary benefits of testing such as information to inform future reproductive decisions and elimination of the "diagnostic odyssey" for parents goes beyond the traditional criteria for NBS tests. A large number of points could be scored

on the survey for such benefits to families in the absence of any perceived benefit to affected children. By contrast, traditional criteria have primarily emphasized benefits to affected children with the recognition that benefits to families are important but secondary. These expanded criteria are not explicitly justified

Sample Population

The report does not specify clearly for what population the survey was intended and why. It states vaguely that "input and opinion were sought from a wide array of child health professionals, subspecialty care experts and individuals interested in newborn screening." The survey was sent to selected individuals and posted on the Web, meaning that a response rate is impossible to determine. The survey itself listed 8 nonexclusive categories of potential respondents with instructions to check off all that apply. Four were categories of providers of screening services, and 3 were providers of health services (diagnostic, primary care, and specialty care). The last category was "consumer." What this means is not clear, because no definition is provided (the actual consumers of NBS tests are newborns). Because the population is not specified, the report's later discussion of the extent to which the sample is "broadly representative" is meaningless.

Respondents were biased toward individuals actively involved in NBS services and lay advocacy groups. In contrast, only 10 primary care providers submitted responses. In addition, the responses per condition were highly variable, with an average of 7 of 84 conditions scored per respondent and 47 ± 20 responses per condition. Therefore, there is no assurance of consistency in the assessments across conditions. Indeed, it is possible for different conditions to have been scored by an entirely different set of respondents.

Literature Review

The literature review lacked the standard methods of analytic framework, key questions, a literature-search strategy, inclusion/exclusion criteria, or systematic assessments of quality of evidence or gaps in evidence. The use of these techniques is now standard professional practice for comprehensive literature reviews. In addition, the literature reviews apparently were conducted by individuals knowledgeable about the draft recommendations derived from the survey. In some cases, the reviewers were members of the ACMG Working Group. This approach does not permit an independent assessment of whether survey results were supported by the literature.

Scope of Report

The report does not fully address a number of key issues including false-positive results, secondary targets, ethical issues, and service-delivery issues. There is inadequate discussion of the anticipated impacts of false-positive results and results of uncertain clinical significance. These outcomes will be common when using a large panel targeting poorly understood conditions.[20] The positive predictive value for MS/MS is estimated to be ~10%,[21] meaning that there are 9 false-positive results for every true positive. False-positive results lead to significant program costs, but, more importantly, harms to unaffected children may result from unnecessary implementation of medications or severely restricted diets. Harm may also come to children with test results of unknown significance who are treated but who ultimately will be found not to have needed intervention. In addition, the literature consistently demonstrates that a subset of parents experience distress and long-term concerns over the health of their child after false-positive NBS results.[22–25] False-positive results and results of unknown significance are expected and tolerable in programs that bring clear benefits to affected children. However, for conditions that are only marginally treatable or untreatable, the negative impacts of NBS programs may outweigh the benefits. That is, NBS programs for some conditions will produce more harm than benefit for children. It is clear that the potential negative impacts of screening must be explicitly balanced with potential benefits on a condition-by-condition basis. The ACMG report does not present these analyses.

The concept of "secondary targets" in the ACMG report is insufficiently developed and justified. Secondary targets are defined as conditions that "are part of the differential diagnosis of a condition in the core panel or are clinically significant and revealed by the screening technology but lack an efficacious treatment (as with some identified through MS/MS technology) or because there are incidental findings for which there is potential clinical significance (hemoglobinopathies)."[1] The report recommends that these results be reported to families but does not advocate that programs provide follow-up services to families. These conditions are not familiar to the vast majority of primary care providers. Management of this information and the conditions themselves (25 in number) will be very challenging for state programs, parents, and primary care providers.

The report reflects no discussion of the ethical and legal issues relevant to a significant expansion of NBS programs. National committees addressing NBS have consistently included detailed discussions of the ethical and social implications of this technology, including 2 National Academy of Sciences reports,[26,27] the AAP/HRSA Newborn Screening Task Force,[2] and the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research.[28] More specifically, with respect to the ACMG Report, there is no discussion of the social, ethical, and legal implications of mandating a large number of new tests within current state programs, including many tests with

uncertain benefits or lack of evidence for health benefit. The silence on these issues is particularly striking given the divergence of this report from the conclusions of such groups as the National Academy of Sciences and the President's Commission.

The limited availability of metabolic specialists in many areas of the United States will be a high barrier to the effective implementation of the ACMG recommendations. It is unclear how programs, families, and primary care providers will manage information generated on a large number of rare and complex conditions without readily available expertise. The ACMG report does not address this concern adequately.

The report also does not adequately address issues of cost-effectiveness. It states that a basic cost-effectiveness study of NBS was conducted and "demonstrated that newborn screening is cost-effective when compared with other recommended medical expenditures," but the report itself does not provide any evidence to support this conclusion. A footnote refers to a commissioned study, but the study has not been released. Reporting only the "bottom line" of a cost-effectiveness study without any supporting analysis violates a fundamental rule of economic evaluation. In this case, there is reason to question whether the study can be rigorous enough to support the strong conclusion. A good cost-effectiveness analysis requires good data, and the report itself refers repeatedly to the limited data available on many variables that are essential to an economic evaluation.

The ACMG statements on cost-effectiveness stand in stark contrast to those of a 2004 report published in the United Kingdom: "Clinical Effectiveness and Cost-Effectiveness of Neonatal Screening for Inborn Errors of Metabolism Using Tandem Mass Spectrometry: A Systematic Review."[29] Using a clearly articulated methodology, the UK researchers were unable to find sufficient data to demonstrate cost-effectiveness of MS/MS technology for conditions other than PKU and medium chain acyl-CoA dehydrogenase deficiency within the UK system. The lack of sufficient data to support policy decisions on expanded NBS is highlighted by other scholars.[30–32]

Finally, recommendations for new programs should follow from a consideration of benefits, risk, and alternatives. In particular, there is no discussion of strategies to enhance clinical detection of conditions as an alternative to population screening. In general, the report reflects no significant effort to balance the competing considerations on a condition-by-condition basis.

These limitations of the ACMG process limit the value of the report for public policy development. We do not believe that the ACMG report provides a sufficient case for initiating expanded mandatory screening for a large number of new conditions for every child in the country. The results and recommendations produced in this work are important contributions to the national dialogue, but they should not be considered the definitive word for major program decisions at the state or federal levels.

EXPANDING NEWBORN SCREENING: PROCEEDING WITH CAUTION

A central problem in the debate over expanded NBS is the lack of information on the efficacy of current NBS programs and the lack of sufficient research about the treatment of the conditions and the impact of screening to clearly justify policy decisions about which tests should be performed and/or disclosed to parents. This problem will be heightened by new technologies. A defining feature of multiplex technologies such as MS/MS is the ability to screen for a wide variety of conditions from a single sample. In the future, DNA-based technology will permit analysis for an even larger number of conditions and genetic susceptibilities using dried blood spots. Given these capabilities, a fundamental problem is whether to manage tests for different conditions on the multiplex panel as separate tests or as a single test package. If programs choose only to disclose results on conditions that clearly meet established criteria, then results on the other conditions, and the potential benefits flowing from those results, will be withheld from families and care providers. On the other hand, offering results on a large number of conditions for which there is limited or no evidence of benefit to affected children may cause harm to some children and families and is likely to be a poor use of scarce resources. This is a legitimate dilemma for which we can offer no easy solution.

Unfortunately, the ACMG report did not address this dilemma. The expert panel assumed an ethical obligation to disclose virtually all results, including those for secondary conditions. The report emphasized the benefits to families even in the absence of benefits to affected children and praised the efficiencies of multiplex testing. These assumptions led to their recommendations to drastically increase the size of NBS programs and, if incorporated into the policy-development process, will lead to further expansion of testing panels as other test modalities come online, such as multiplex DNA analysis. Continuing to expand test panels simply because we can easily add new tests with potential value does not constitute a prudent approach to public policy. We propose the alternative of moving forward with the expansion and development of NBS programs under a research paradigm that will answer the critical questions about the benefits and costs within a reasonable time period.

Research is needed to evaluate the benefits and risks of early detection by NBS programs. The AAP/HRSA Newborn Screening Task Force explicitly called for research to evaluate NBS technology and noted that "[s]ince the 1960's, decisions about which tests to use in newborn screening programs often have been made in an extemporaneous fashion, depending on recommen-

dations from professional groups, patient advocates, state legislators, and newborn screening programs.[references deleted]…. Surveillance and research are essential to provide the evidence needed for state-level decisions and nationally recognized standards." The ACMG report[1] also endorses long-term data collection and surveillance to enhance NBS systems, although this recommendation was not highlighted, nor has it been emphasized in subsequent policy discussions. Research in this domain should include both the evaluation of the clinical and psychosocial impact of screening on affected individuals and infants with false-positive results. To date, the only placebo-controlled clinical trial of an NBS program in the United States is the Wisconsin Cystic Fibrosis Trial.[33] Although randomized, controlled trials of NBS can be justified in some cases,[34,35] in other cases when the natural history of a condition is well understood and there are serious consequences that can be avoided by early detection, other research designs may be appropriate.

As noted, the research foundation for the treatment of rare genetic conditions is poor.[32,35] This situation is the result of the inherent difficulties in acquiring outcome data on the treatment of rare conditions. The fact remains that affected children detected through NBS programs are not enrolled routinely or commonly in research protocols in which treatment approaches can be compared or in which short-term or long-term outcomes can be measured. Affected children are treated according to the preference of the local or regional service providers. Therefore, many published studies are based on small numbers of children in uncontrolled protocols. The belief of treating physicians that these children are doing better than historical experience is important information, but the possibilities of bias when using historical controls are numerous. A recent literature review by Steiner[36] found that the clinical approach to most metabolic conditions detected by NBS is not evidence-based. He concludes: "Treatment of IEM [inborn errors of metabolism] has historically been based to a large degree on pathophysiologic and biochemical mechanisms of disease coupled with clinical experience. A cynic might say that treatment for IEM has been based on anecdote, conjecture, theory, and tradition. Clinicians treat IEM as they were taught, with a few modifications based on clinical judgment and personal experience. As a result, evidence base in sorely needed in the field." If expanded NBS moves rapidly into implementation in state programs, arguments and uncertainties will persist indefinitely about the benefits and costs of programs and over the best way to care for affected children.

RECOMMENDATIONS

The most appropriate way to develop public policy would be to revisit the questions addressed by the ACMG but with a strengthened methodology and attention to a broader set of issues. However, the ACMG has been supported by several professional and lay organizations, and many states are actively implementing expanded NBS programs using MS/MS technology. Nevertheless, given the weaknesses in the methodology used to generate the ACMG recommendations, they should not be considered the "standard of care" for state programs. The ACMG report does not provide convincing arguments or data to conclude that the recommended panel is optimal for child welfare or the most effective use of scarce resources. Where does this leave state programs and federal agencies working toward policy decisions? We offer 4 recommendations to move forward with NBS programs while addressing the lack of adequate information.

Recommendation 1

The implementation of expanded NBS panels should be conducted within a research paradigm.[32,37] Research protocols could be regional or national in scope. Such an approach would encourage or require uniformity in case definition, standardization of initial treatment protocols, and thorough, consistent follow-up. Careful effort must be given to both medical and social outcomes for infants with rare disorders who are identified with and without screening (taking advantage of differences in state testing panels) and for infants with false-positive tests. Data on other conditions that go beyond the ACMG recommendations should also be collected (eg, glucose-6-phosphate dehydrogenase screening in Washington, DC; HIV screening in New York and Connecticut). By pooling data on a regional or national basis, information could be acquired on program benefits, harms, and costs with a sufficient number of affected children to inform NBS policy decisions. A variety of research strategies could be used, but all protocols should include careful attention to safety and rights of research participants as well as quality of outcome measures. This approach permits the use of promising but unproven approaches to screening while not opening programs to the indefinite use of ineffective or harmful technologies.

Recommendation 2

Treatment protocols for conditions targeted by NBS programs should be coordinated and evaluated on a regional or national basis through cooperative group trials. The Children's Oncology Group offers an excellent model.[38] Substantial gains have been made in pediatric cancer care because of the development of national protocols for the treatment of rare cancers in children. New ideas in treatment can be debated by experts, implemented, and evaluated in a rigorous manner using current consensus treatments as the control group. Again, pooling data obtained in a consistent fashion for these rare conditions is essential to making gains in treatment

approaches. In addition, regional or national experience in monitoring or managing conditions of unknown clinical significance is critical in determining whether such conditions need managing or monitoring.

Recommendation 3

A conference or working group, perhaps under the auspices of the Institute of Medicine, should be held to consider the public policy, health services, and ethical issues related to multiplex technologies. The eventual goal of a research-paradigm NBS program is to determine if the uniform panel is clinically useful and valid. As part of the evaluation, one needs to define and delineate these responsibilities. A focus specifically on MS/MS and DNA-based technologies could result in recommendations on several key issues: How should technology be evaluated from a public health and community perspective, and how should this evaluation influence the expansion or contraction of conditions on the uniform panel? What is the responsibility of programs to disclose results on conditions that do not meet established criteria for screening programs? What is the responsibility of programs to disclose or not disclose results of uncertain clinical significance? What are the roles of the medical home and NBS program in managing the disclosure of results to parents for secondary conditions and conditions of unknown clinical significance? Is it ethically justifiable to "mandate" screening for conditions that do not meet traditional criteria? What are the legal liabilities for decisions not to disclose selected results obtained through multiplex technologies? A thorough analysis of these and related concerns would provide much-needed guidance to NBS programs as they struggle with new technical capabilities, legal challenges, and public pressures.

Recommendation 4

With the accumulated data and ethical and policy analysis from the prior recommendations, an independent and impartial organization should provide a forum for comprehensive policy recommendations about NBS. Although this final recommendation is future-oriented, it may be valuable to articulate a long-term process so that the initial research and policy deliberations can proceed with the goal in mind.

Implementing these recommendations will require an unprecedented degree of collaboration between states and a larger role for the federal government in NBS than has been the case historically. It is clear that funding of this research will require a significant new federal financial commitment as well. However, NBS programs are vitally important to the welfare of children, and they should not be expanded without mechanisms in place to evaluate their safety and efficacy.

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MEDICARE: DISCUSS EVIDENCE-BASED MEDICINE

"Medicare is now enrolling patients in . . . trials or registries, examining the effectiveness of a wide range of expensive and popular treatments and procedures – new cancer drugs, defibrillators, PET scans to detect early Alzheimer's disease and, possibly, home oxygen therapy for emphysema. These are often costly treatments – Medicare paid $1.2 billion for defibrillators in 2002, for example, according to Medtronic, which makes the devices. No matter what those studies end up showing, the use of clinical trials can make them controversial even at the outset. The very nature of a clinical trial means that only some patients actually receive the new treatment, while others, for comparison's sake, do not. Paying for some patients but not others to receive a new treatment is a stark departure for Medicare."

Kolata G. *New York Times*. March 3, 2006
Noted by JFL, MD